This Month in Genetics

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X Chromosome Inactivation at Single-Cell Resolution

X chromosome inactivation (XCI) in females is random, or is it? The selection of the X to be inactivated is set early in the embryo and, as far as we know, is a chance event overall. Particularly because XCI occurs so early in embryogenesis, the initial random selection of the X to be inactivated does not necessarily translate into complete randomness throughout the body. Different tissues arise from different embryonic layers, after all, and certain cell types have very specific migration and differentiation processes that will govern their location relative to the cells from which they originate. To understand XCI patterns at a resolution previously unachieved, a group led by Jeremy Nathans inserted a different fluorescent reporter into each copy of the X-linked gene *Hprt*, creating heterozygous female mice with red cells in which one X was active and green cells in which the other X was active. The striking images in this paper illustrate the variability in XCI patterns that can be found within siblings and between tissues, and they also show examples of left-right asymmetry for XCI within an individual. The two-color system allowed the authors to sort cells on the basis of the active X in order to measure gene expression from the inactive X. They also explored XCI in the content of an X-linked mutation to determine how XCI patterns influence phenotypic expression at a local level.

Wu et al. (2014). Neuron 81, 103–119.

Alpha-1 Antitrypsin Regulates TNF-α Signaling

Although apparently quite underdiagnosed, α-1 antitrypsin deficiency (AATD) is a significant contributor to chronic obstructive pulmonary disease and is one of the most common single-gene disorders. AAT is a natural inhibitor of several serine proteases, and it is believed that when it is deficient, the relative excess of these proteases leads to lung damage. New data from Bergin et al. suggest that inflammation might also contribute to the pathogenesis of AATD in ways that were not previously appreciated. They discovered that AAT regulates proinflammatory tumor necrosis factor α (TNF-α) and downstream neutrophil signaling. In AATD patients, increased activation of the TNF-α system yields a release of granule proteins from neutrophils and an increased incidence of autoantibodies to one of these granule proteins, lactoferrin. Intravenous augmentation therapy with purified human AAT has been used to treat AATD with the idea that it will bring the inhibitor-protease ratio back into balance and potentially slow the progression of lung disease. Bergin et al. also show that this treatment is associated with decreases in TNF-α signaling and in the levels of the lactoferrin autoantibodies. This new view of AATD pathogenesis might also have implications for other diseases that involve TNF-α misregulation.

Bergin et al. (2014). Sci. Transl. Med. 6, 217ra1.

Releasing the Ring

Human cells don't do well with circularized chromosomes, which are known as ring chromosomes. Picture the alignment of X-shaped chromosomes attached to spindle fibers—the distorted shape of a ring chromosome makes it difficult for the chromosome to proceed through these normal meiotic and mitotic processes, leaving them unstable. The typical result of this instability is an aneuploid cell. To better understand ring-chromosome instability, Bershteyn et al. tried to generate induced pluripotent stem cells from fibroblasts containing a ring chromosome 17. The majority of cells in the resulting successful clones had 46 chromosomes, including two copies of chromosome 17, but lacked the ring 17. Did the ring open up, yielding a linear structure, or was there something else going on? SNP microarrays revealed homozygosity across chromosome 17, thereby clarifying the mechanism: when the ring was lost, a compensatory duplication of the other chromosome 17 led to uniparental disomy, normalizing the gene dosage across the chromosome. A similar result was observed when they started with a ring chromosome 13, so it is not unique to chromosome 17 and might be a useful tool for understanding the regulation of chromosome number.

Bershteyn et al. (2014). Nature. Published online January 12, 2014. http://dx.doi.org/10.1038/nature12923.

Factors Associated with the Outcome of 22q11.2 Deletion Syndrome

Although not unique to the syndrome, 22q11.2 deletion is one of the recurrent pathogenic copy-number variants with reduced penetrance and variable expression. One such variable feature is intellectual ability; although many people with 22q11.2 deletion syndrome have a learning disability, only about 10% have moderate to severe intellectual disability. Considering that 85% of

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patients have a nearly identical deletion, the size of the deletion is not the key to this variable expression. Looking for alternative explanations, Cheung et al. explored whether clinical features might be correlated with intellectual disability in a group of adults with 22q11.2 deletion syndrome. Logistic regressions uncovered neonatal hypocalcemia as a predictor of intellectual disability. This link seems to occur because hypocalcemia causes neonatal seizures, which themselves can lead to long-term neurodevelopmental issues. Currently, the hypocalcemia in 22q11.2 deletion syndrome is generally considered self-resolving; the link with intellectual disability led the authors to argue for early recognition and management of the hypocalcemia as a potential way to reduce the likelihood of severe intellectual disability in people with 22q11.2 deletion syndrome.

Cheung et al. (2014). Genet. Med. 160, 40-44.

Meta-analysis of Rare Variants

Meta-analyses of common genetic variation generated some of the major success stories from genome-wide association studies. As researchers begin to seek rare genetic variation that might also contribute to complex traits, new approaches are needed so that data from multiple studies can be combined easily, particularly given the massive sample sizes that will be needed for finding these associations. Gonçalo Abecasis and colleagues have developed a freely available and flexible method of identifying rare-variant associations. With a real data set of more than 18,000 individuals, they sought rare-variant associations with blood lipid levels as a quantitative trait and show that their method is powerful and can detect associations with many previously identified loci.

Liu et al. (2013). Nat. Genet. Published online December 15, 2013. http://dx.doi.org/10.1038/ng.2852.

This month in Our Sister Journals

Personalized Gene Expression

Both genetic and nongenetic factors are likely to influence the expression level of individual genes. To identify these factors, many have used the average expression level of a gene as the phenotype of interest. Wang et al. looked at this problem a little bit differently. They wanted to find expression loci that influence the *variance* of gene expression in a population. They found them by using gene expression data from a twin cohort, which provided a nice immediate way of validating their results with data from the matched twin. The sample also allowed them to disentangle the genetic and environmental effects that contribute to the expression differences. Considering gene expression as a complex trait, this provides a nice model for thinking about the ways in which multiple inputs combine to influence one phenotypic variable.

Wang et al. (2013). Genetics. Published online December 2, 2013. http://dx.doi.org/10.1534/genetics.113.157503.